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Pharmacokinetics of Oral Doxycycline during Combination Treatment of Severe Falciparum Malaria

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The pharmacokinetics of oral doxycycline administered at 200 mg every 24 h were investigated in 17 patients recovering from severe *Plasmodium falciparum* malaria. The data suggest that the doses of doxycycline currently recommended (circa 3.5 mg/kg of body weight daily) may not be optimal.

Oral doxycycline, a lipophilic bacteriostatic antibiotic, is the recommended secondary oral antimalarial treatment during the recovery of nonpregnant adults from severe *Plasmodium falciparum* malaria. It is combined with primary parenteral treatments to ensure the clearance of all remaining parasites and to prevent the emergence of resistance to the primary antimalarial. There is no published information on the pharmacokinetics of doxycycline in patients with severe malaria, or indeed with any infectious disease, and the recommended dosage regimens currently used are empirical; they include 3 mg/kg of body weight/day, 100 mg every 12 or 24 h, and 200 mg every 24 h, with or without a loading dose (1, 2, 27, 28).

In healthy volunteers who have taken oral doxycycline, the maximum doxycycline plasma concentrations (C_{max}) of 1.5 to 7.0 μg/ml are usually reached within 3 h, and the drug has a half-life of 14 to 24 h (16, 26). Concurrent ferrous sulfate, antacids, phenobarbital, heavy alcohol intake, and undernutrition are known to accelerate the clearance of doxycycline (11, 12, 13, 15, 16, 21). It is not known whether the pharmacokinetics of doxycycline are affected by same-day ferrous sulfate or malaria, and there is little information on the in vitro sensitivity of *P. falciparum* parasites to doxycycline (3, 8, 18, 23). It is not appropriate to assess the pharmacodynamic effects of doxycycline alone in vivo, as the drug should not be used alone. In combination, the antimalarial effect of the primary parenteral drugs predominates. The optimum dosage can be determined only from comparisons of the pharmacokinetics and by extrapolations from in vitro parasite sensitivity assessments.

The study was conducted from 1999 to 2002 at Mae Sot Hospital, Tak Province, western Thailand from May to July and November to December of each year. Patients aged 16 to 65 years were included if they or an attending relative were able and willing to give informed written consent and if they had slide-confirmed, single species *P. falciparum* parasitemia; no contraindications to doxycycline; a negative pregnancy test for females of reproductive age; no requirement for interacting drugs (warfarin, bismuth, antacids, aluminum, magnesium, calcium, iron, zinc salts, or sucralfate); and clinically severe malaria (14, 29). Ethical clearance was granted by the Ministry of Public Health, Government of Thailand.

Patients were randomized to receive either intravenous artesunate (Guilin No. 2 Pharmaceutical Factory, Guangxi, People's Republic of China) at 2.4 mg/kg of body weight, followed by 1.2 mg of artesunate/kg 12 h later and then 1.2 mg of artesunate/kg/day, or quinine dihydrochloride (Government Pharmaceutical Organization, Bangkok, Thailand) at 20 mg of salt/kg as a loading dose infused over 4 h, followed by 10 mg of salt/kg infused over 2 h three times a day. When patients were able to take tablets, either oral artesunate, to a total intravenous and oral dose of 12 mg/kg or quinine sulfate (Government Pharmaceutical Organization), at 10 mg of salt/kg every 8 h, was given for a total treatment course of 7 days. This regimen was supplemented with doxycycline (Vibramycin, 100-mg capsules; Pfizer) at 200 mg/day at 0800 h for 7 days.

Patients were allotted ferrous sulfate (200 mg) either at 1300 and 1800 h or every 12 h after the 7-day course of doxycycline. The first six patients were designated ad hoc, while the remaining 11 patients were randomly placed in one of the two ferrous sulfate treatment groups. The choice of treatment group was kept in an opaque envelope, which was opened only after the patient consented to the study. Patients were counseled to take all drugs as prescribed.

Blood samples for hematocrit and parasitemia tests and biochemistry were taken from the patients on admission. Axillary temperature, hematocrit, and parasite counts were measured every 6 h until parasite clearance (14). When the patient was able to eat, doxycycline was started. Four milliliters of venous blood was taken at 0, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h after doxycycline administration. Plasma samples were stored at −30°C until analysis. After liquid-solid extraction with a Bond Elut C18 cartridge, the plasma doxycycline concentration was determined by reverse-phase high-performance liquid chromatography with UV detection (19), by using demeclocycline as the internal standard. The lower limit of

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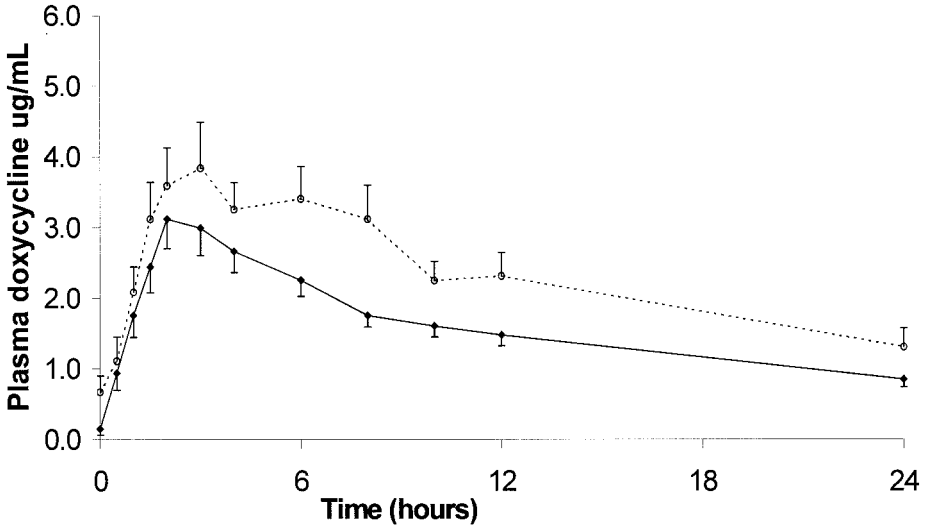

FIG. 1. Relationship between plasma doxycycline concentration and time after the first (solid line) and last (broken line) 200-mg doxycycline doses.

quantification was 25 ng/ml and the intra- and interassay coefficients of variation were lower than 3 and 6.7%, respectively.

Observed plasma doxycycline concentrations (C_{max}) and time to C_{max} (T_{max}) were used, and the area under the curve from 0 to 24 h ($AUC_{0\rightarrow24}$) was calculated by using the linear trapezoidal rule, with log-linear extrapolation to infinity for $AUC_{0\rightarrow\infty}$ (22) (Fig. 1). The AUC after the dose on day 7 was also adjusted by subtracting the AUC calculated from the day 7 trough and the elimination rate constant. The mean residence time, clearance, and volume of distribution for day 7 were calculated by using this adjusted estimate of AUC. A noncompartment model was used (Model 200, WinNonlin 3.1; Pharsight Corp., Cary, N.C.). Clearance was calculated as dose/$AUC_{0\rightarrow\infty}$. The antimalarial drug susceptibilities of fresh *P. falciparum* isolates to doxycycline were determined by using the microdilution radioisotope method (incubation for 48 h in the presence of 5% O_2, 5% CO_2, and 90% N_2), from a population similar to that from which the patients recruited to this study came, at the Shoklo Malaria Research Unit, Mae Sot, Thailand (4).

Seventeen patients were recruited to the study during their recovery from severe malaria (Table 1). The median interval between admission and start of oral doxycycline was 4 days (range, 0 to 7 days). Phenobarbital (a 200-mg intramuscular dose) was given for a median of 4 days (range, 0 to 6 days) before the first dose of doxycycline for nine patients. Two patients vomited within 30 min of the first dose of doxycycline and were successfully redosed 24 h later. All patients completed the full course of doxycycline. The median parasite clearance time was 66 h (range, 36 to 84 h). All patients survived, and 10 were again in attendance at the hospital on the morning of the seventh doxycycline dose.

Median serum bicarbonate levels were 21 (range, 20 to 27) and 25 (range, 22 to 28) mmol/liter, creatinine levels were 64 (range, 48 to 680) and 64 (range, 48 to 528) μmol/liter, urea levels were 12.7 (range, 5.3 to 64.1) and 9.6 (range, 5.5 to 45.3) mmol/liter, and total bilirubin levels were 8.9 (range, 2.2 to 18.9) and 7.8 (range, 2.2 to 9.0) μmol/liter on the first and last days, respectively. Serum bilirubin, creatinine, and urea levels were significantly higher, and serum bicarbonate levels were significantly lower, on admission than on the day of the first doxycycline dose ($P \leq 0.02$). After acute administration, the median elimination half-life was 10.5 h (range, 6.9 to 17.9 h) (Table 2). Although the sample size was small, there were no significant differences in the pharmacokinetic parameters between those who did and did not have ferrous sulfate ≥5 h after the doxycycline. Before the seventh doxycycline dose was administered, the median trough plasma doxycycline was 0.56 μg/ml (range, 0 to 2.28 μg/ml). The actual and adjusted C_{max}, $AUC_{0\rightarrow24}$, and $AUC_{0\rightarrow\infty}$ after the last dose were not significantly larger than these measures after the first dose ($P > 0.05$). The median ratio of unadjusted $AUC_{0\rightarrow24}$ between that after the seventh doses and first doses was 1.2 (range, 0.5 to 2.8). The 24-h accumulation index (22) was 1.26.

Of 633 *P. falciparum* isolates from primary infections collected in 2001 to 2004, the geometric mean (95% confidence interval [CI]) of the 50% effective concentration (EC_{50}) was 4.86 μg/ml (range, 4.58 to 5.15 μg/ml) (equivalent to 10.1 μmol/liter [range, 9.5 to 10.7 μmol/liter]). After the first and last dose of doxycycline, three and four patients, respectively, had a C_{max} exceeding the estimated EC_{50}. In comparison to previous reports on the pharmacokinetics of doxycycline, the C_{max}, T_{max}, and volume of distribution described here are similar, but the half-life was relatively short at 10.5 h (16, 26). Neither acute malaria nor concurrent ferrous sulfate given ≥5 h after doxycycline apparently altered doxycycline pharmacokinetics. Potential problems with the study include the small sample size and potential suboptimal adherence to doxycycline and ferrous sulfate regimens. However, pill counts on day 7 suggested that all medication had been taken and that the study would reflect a real-life situation without observed therapy.

The geometric mean for the *P. falciparum* doxycycline EC_{50} of 10.1 μmol/liter described here is similar to those in previous reports from Senegal (18) and western Thailand (23) but double those described for isolates from Cambodia and West Af-

TABLE 1. Clinical and laboratory details of study patients at admission

Variable	Results for patients[a]			*P*
	All	Without iron	With iron	
No. of patients	17	8	9	
Body weight (kg)	48.8 (38.5–61.0)	51 (38.5–58)	48.8 (46.0–61.0)	1.0
No. of males	14	7	7	1.0
Age (yr)	30 (18–59)	34 (20–41)	28 (18–59)	0.4
No. of categories of severe malaria per patient	1.5 (1–6)	2 (1–5)	1 (1–4)	0.4
No. of days ill	5 (2–14)	5 (2–10)	4 (2–14)	0.6
Temp (°C)[b]	37.7 (37.0–38.3)	37.8 (36.7–38.8)	37.6 (36.6–38.5)	0.8
Glasgow Coma score	10 (6–15)	8.5 (6–15)	10 (6–15)	0.3
Parasitemia (μl)[c]	21,262 (2,680–168,655)	12,880 (163–1,016,015)	29,696 (1,794–168,655)	0.7
Trophozoites and schizonts (%)	35 (0–68)	42 (17–66)	2 (0–68)	0.3
Hematocrit (%)	34 (14–46)	30 (14–46)	27 (14–42)	0.8
Plasma glucose (mmol/liter)[d]	8.6 (2.6–16.2)	9.5 (5.3–14.5)	8.4 (2.6–16.2)	0.6
Plasma lactate (mmol/liter)[e]	3.5 (1.0–22.1)	5 (1.0–22.1)	2.7 (1.2–12.1)	0.7
Serum creatinine (μmol/liter)[f]	108 (56–680)	110 (56–680)	108 (56–184)	0.8
Serum urea (mmol/liter)[g]	40.0 (6.0–95.3)	31.3 (18–80.8)	45 (5.5–95.3)	0.4
Total serum bilirubin (μmol/liter)[h]	38.9 (2.2–173.2)	40.0 (12.2–104.3)	38.9 (2.2–173.2)	0.9
Serum bicarbonate (mmol/liter)[i]	19.7 (10.0–29.0)	19.4 (13.4–24.0)	21.0 (10.0–29.0)	0.3
Parasite clearance time/h	66 (36–84)	78 (64–84)	66 (36–84)	0.2
Parasite clearance, 50%/h	8.5 (0.3–37.2)	11.8 (1.3–22.5)	8.5 (0.3–37.2)	0.8
Parasite clearance, 90%/h	29.0 (5.8–57.5)	35.0 (21.8–57.5)	22.5 (5.8–55.4)	0.3

[a] Medians (ranges) are given unless otherwise noted.
[b] Mean (95% CI).
[c] Geometric mean (95% CI). (Number of asexual parasites/1,000 erythrocytes on thin film × hematocrit % × 125.6 or number of asexual parasites/200 white cells on thick film assuming a white cell count of 8×10^9/liter).
[d] Normal range, 3.5 to 5.5 mmol/liter.
[e] Normal, <4 mmol/liter.
[f] Normal range, 70 to 150 μmol/liter.
[g] Normal range, 2.5 to 6.7 mmol/liter.
[h] Normal range, 3 to 17 μmol/liter.
[i] Normal range, 21 to 28 mmol/liter.

rica (3). The MICs of doxycycline for *P. falciparum* after 96 h of incubation are 4- to 20-fold lower than those after 48 h of incubation (18, 30), and EC_{50}s are lower at higher oxygen tension (7, 16). The in vitro incubation period (48 h) and oxygen tension (5%) used here introduce potential confounding factors. Therefore, at present, it is difficult to interpret in vitro sensitivity data for doxycycline. These data indicate that present dosing might be inadequate for some patients and that,

TABLE 2. Doxycycline pharmacokinetic parameters after acute and convalescent oral doxycycline administration[a]

Variable	Result for patient group indicated					
	Acute			Convalescence		
	All	Without iron	With iron	All	Without iron	With iron
No. of patients	17	8	9	10	5	5
Doxycycline dose (mg/kg)	4.1 (3.3–5.2)	4.0 (3.5–5.2)	4.1 (3.3–4.4)	4.1 (3.5–4.6)	3.6 (3.5–4.3)	4.2 (4.1–4.6)
T_{max} (h)	2 (1.5–4)	2 (1.5–4)	3 (2–4)	3 (1.5–8)	3 (1.5–8)	3 (2–6)
C_{max} (μg/ml)	3.17 (1.63–7.72)	3.32 (1.63–5.29)	3.17 (2.30–7.72)	4.44 (1.52–8.64)	5.36 (3–6.58)	4.0 (1.52–8.64)
No. of patients with a C_{max} of >4.9 μg/ml (total no. tested)	3 (17)	1 (17)	2 (17)	4 (10)	3 (10)	1 (10)
Adjusted C_{max} (μg/ml)[b]				3.86 (1.46–8.05)	4.65 (2.70–6.20)	3.36 (1.46–8.05)
$AUC_{0\to\infty}$ (μg · h/ml)	49.6 (25.1–140.1)	42.5 (25.1–140.1)	51.5 (40.9–134.2)	73.0 (29.3–182)	84.8 (49.3–182)	61.6 (29.3–144.5)
Adjusted $AUC_{0\to\infty}$ (μg · h/ml)[b]				70.1 (29.0–145)	77.9 (47.0–145)	60.8 (29.0–138.3)
$AUC_{0\to24}$ (μg · h/ml)[b]	32.0 (18.7–79.7)	28.8 (18.7–63.4)	33.3 (25.4–79.7)	48.6 (18.3–69.8)	49.3 (34.3–69)	44.5 (18.3–69.8)
Number points for half-life calculation	8 (5–9)	8 (5–9)	7 (5–8)	7 (4–9)	7 (4–9)	7 (5–8)
Elimination half-life (h)	10.5 (6.9–17.9)	10.2 (9.3–17.9)	11.0 (6.9–16.6)	11.6 (8.5–17.2)	11.7 (9.8–17.0)	11.5 (8.5–17.2)
Apparent volume of distribution (ml/kg)[b]	1,451 (619–2,984)	1,690 (757–2,984)	1,157 (619–1,917)	979 (534–2,675)	834 (534–1,533)	1,180 (550–2,675)
Apparent clearance (Cl/f) (ml/kg/h)[b]	90 (37–221)	112 (42–221)	71 (37–112)	63 (31–156)	52 (31–93)	68 (48–156)
Mean residence time (h)[b]	16.6 (11.5–27.1)	16.3 (15.1–27.1)	17.2 (11.5–26.6)	18.4 (10.0–59.3)	18.0 (15.0–59.3)	18.8 (10.0–31.4)
Day 7 trough doxycycline concentration (μg/ml)				0.56 (0–2.28)	0.78 (0–2.28)	0.15 (0.06–1.39)

[a] Values were determined on day 0 for the acute group and on day 7 for the convalescent group after oral administration of 200 mg of doxycycline. Medians (ranges) are shown unless otherwise indicated. There were no differences ($P < 0.05$) between variables for acute and convalescent groups and for groups with and without ferrous sulfate. To convert doxycycline concentration (μg/ml) to mmol/liter, multiply by 2.08.
[b] Convalescent data for these variables were adjusted by subtracting the AUC calculated by using plasma doxycycline trough concentration immediately before the last dose and by log-linear extrapolations to infinity by using the observed half-life.

with a doxycycline half-life of 10.5 h, twice daily dosing may be more appropriate. A loading dose of twice the maintenance dose (i.e., 400 mg) would allow plasma doxycycline concentrations to rise above a therapeutic level quickly (22). Although doses of up to 600 mg of doxycycline may be well tolerated when taken with food and water (9), patients recovering from severe disease frequently have difficulty eating.

Without reliable information on the relationship between plasma concentration of doxycycline and the therapeutic response, and thus on which pharmacokinetic variable is most strongly associated with pharmacodynamic response, doubt will remain as to the optimum regimen. There is limited clinical trial evidence that doxycycline is an effective companion drug to quinine or the artemisinin derivatives in the treatment of uncomplicated or severe malaria (5, 6, 10, 17, 20, 24, 25). Longitudinal monitoring of the sensitivity of *P. falciparum* to doxycycline and further investigation of doxycycline pharmacokinetic-antimalarial pharmacodynamic interrelationships, the tolerability of higher doses, adherence, and standardization of methods will be important to ensure that the correct dose of doxycycline is used in combination therapy.

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REFERENCES

1. **Anonymous.** 1998. Drugs for parasitic infections. Med. Lett. **40:**1–12.
2. **Anonymous.** 2000. British National Formulary No. 39. British Medical Association and the Royal Pharmaceutical Society of Great Britain, London, United Kingdom.
3. **Basco, L. K., and J. Le Bras.** 1993. Activity in vitro of doxycycline against multidrug-resistant *Plasmodium falciparum*. Trans. R. Soc. Trop. Med. Hyg. **87:**469–470.
4. **Brockman, A., R. N. Price, M. van Vugt, D. G. Heppner, D. Walsh, P. Sooklo, T. Wimonwaltrawatee, S. Looareesuwan, N. J. White, and F. Nosten.** 2000. *Plasmodium falciparum* antimalarial drug susceptibility on the northwestern border of Thailand during five years of extensive artesunate-mefloquine use. Trans. R. Soc. Trop. Med. Hyg. **94:**537–544.
5. **Chin, W., and R. Intraprasert.** 1973. The evaluation of quinine alone or in combination with tetracycline and pyrimethamine against falciparum malaria in Thailand. Southeast Asian J. Trop. Med. Public Health **4:**245–249.
6. **Colwell, E. J., R. L. Hickman, and S. Kosakal.** 1972. Tetracycline treatment of chloroquine-resistant falciparum malaria in Thailand. JAMA **220:**684–686.
7. **Divo, A. A., T. G. Geary, and J. B. Jensen.** 1985. Oxygen- and time-dependent effects of antibiotics and selected mitochondrial inhibitors on *Plasmodium falciparum* in culture. Antimicrob. Agents Chemother. **27:**21–27.
8. **Fivelman, Q. L., J. C. Walden, P. J. Amith, P. I. Folb, and K. I. Barnes.** 1999. The effect of artesunate combined with standard antimalarials against chloroquine-senstitive and chloroquine-resistant strains of *Plasmodium falciparum in vitro*. Trans. R. Soc. Trop. Med. Hyg. **93:**429–432.
9. **Marlin, G. E., and S. Cheng.** 1979. Pharmacokinetics and tolerability of a single oral 600-mg dose of doxycycline. Med. J. Aust. **1:**575–576.
10. **Metzger, W., G. Mordmuller, W. Graninger, U. Bienzle, and P. G. Kremsner.** 1995. High efficacy of short term quinine-antibiotic combinations for treating adult malaria patients in an area in which malaria is hyperendemic. Antimicrob. Agents Chemother. **39:**245–246.
11. **Neuvonen, P. J., and O. Penttila.** 1974. Effect of oral ferrous sulphate on the half-life of doxycycline in man. Eur. J. Clin. Pharmacol. **7:**361–363.
12. **Neuvonen, P. J., and O. Penttila.** 1974. Interaction between doxycycline and barbiturates. BMJ **i:**535–536.
13. **Neuvonen, P. J., O. Penttila, M. Roos, and J. Tirkkonen.** 1976. Effect of long-term alcohol consumption on the half-life of tetracycline and doxycycline in man. Int. J. Clin. Pharmacol. **14:**303.
14. **Newton, P. N., B. J. Angus, W. Chierakul, A. Dondorp, R. Ruangveerayuth, K. Silamut, P. Teerapong, Y. Suputtamongkol, S. Looareesuwan, and N. J. White.** 2003. Randomized comparison of artesunate and quinine in the treatment of severe falciparum malaria. Clin. Infect. Dis. **37:**7–16.
15. **Nguyen, V. X., D. E. Nix, S. Gillikin, and J. J. Schentag.** 1989. Effect of oral antacid administration on the pharmacokinetics of intravenous doxycycline. Antimicrob. Agents Chemother. **33:**434–436.
16. **Perdue, B. E., and H. C. Standiford.** 1999. Tetracyclines, p. 981–995. *In* V. L. Yu, T. C. Merigan, Jr., and S. L. Barriere (ed.), Antimicrobial therapy and vaccines. Williams & Wilkins, Baltimore, Md.
17. **Ponnapalam, J. T.** 1981. Doxycycline in the treatment of falciparum malaria among aborigine children in West Malaysia. Trans. R. Soc. Trop. Med. Hyg. **75:**372–377.
18. **Pradines, B., A. Spiegel, C. Rogier, A. Tall, J. Mosnier, T. Fusai, J. F. Trape, and D. Parzy.** 2000. Antibiotics for prophylaxis of *Plasmodium falciparum* infections: in vitro activity of doxycycline against Senegalese isolates. Am. J. Trop. Med. Hyg. **62:**82–85.
19. **Prevosto, J. M., B. Beraud, V. Cheminel, Y. Gaillard, C. Mounier, and J. F. Chaulet.** 1995. Determination of doxycycline in human plasma and urine samples by high performance liquid chromatography. Application for drug monitoring in malaria chemoprophylaxis. Ann. Biol. Chem. **53:**29–32.
20. **Pukrittayakamee, S., A. Chantra, S. Vanijanonta, R. Clemens, S. Looareesuwan, and N. J. White.** 2000. Therapeutic responses to quinine and clindamycin in multidrug-resistant falciparum malaria. Antimicrob. Agents Chemother. **44:**2395–2399.
21. **Raghuram, T. C., and K. Krishnaswamy.** 1982. Pharmacokinetics and plasma steady state levels of doxycycline in undernutrition. Br. J. Clin. Pharmacol. **14:**785–789.
22. **Rowland, M., and T. N. Tozer.** 1995. Clinical pharmacokinetics: concepts and applications. Lippincott Williams & Wilkins, Philadelphia, Pa.
23. **Sponer, U., S. Prajawong, G. Wiedermann, H. Kollaritsch, G. Wernsdorfer, and W. H. Wernsdorfer.** 2002. Pharmacodynamic interaction of doxycycline and artemisinin in *Plasmodium falciparum*. Antimicrob. Agents Chemother. **46:**262–264.
24. **Taylor, W. R. J., H. Widjaja, T. L. Richie, H. Basri, C. Ohrt, E. Tjitra, E. Taufik, T. R. Jones, K. C. Kain, and S. L. Hoffman.** 2001. Chloroquine/doxycycline combination versus chloroquine alone and doxycycline alone for the treatment of *Plasmodium falciparum* and *Plasmodium vivax* malaria in northeastern Irian Jaya, Indonesia. Am. J. Trop. Med. Hyg. **64:**223–228.
25. **Watt, G., L. Loesuttiviibool, G. D. Shanks, E. F. Boudreau, A. E. Brown, K. Brown, K. Pavanand, H. K. Webster, and S. Wechgritaya.** 1992. Quinine with tetracycline for the treatment of drug-resistant falciparum malaria in Thailand. Am. J. Trop. Med. Hyg. **47:**108–111.
26. **Welling, P. G., P. A. Koch, C. L. Curtis, and W. A. Craig.** 1977. Bioavailability of tetracycline and doxycycline in fasted and nonfasted subjects. Antimicrob. Agents Chemother. **11:**462–469.
27. **Wernsdorfer, W. H.** 1997. Antimalarial drugs, p. 151–198. *In* G. Carosi and F. Castelli (ed.), Handbook of malaria infection in the tropics. AIFO, Bologna, Italy.
28. **White, N. J.** 2003. Malaria, p. 1205–1295. *In* G. C. Cook and A. Zumla (ed.), Manson's tropical diseases. Saunders, London, United Kingdom.
29. **World Health Organization.** 1990. Severe and complicated malaria. Trans. R. Soc. Trop. Med. Hyg. **84**(Suppl. 2)**:**S1–S65.
30. **Yeo, A. E. T., and K. H. Rieckmann.** 1995. Increased antimalarial activity of azithromycin during prolonged exposure of *Plasmodium falciparum* in vitro. Int. J. Parasitol. **25:**531–532.